of Clinical Chemistry, University Hospital, Robert Koch-Str. 8, D-89070 Ulm in Germany. See paragraph 1 of the Declaration, and the copy of his Curriculum Vitae attached to the Declaration. Professor Grünert is an inventor in the present application.

As stated by Professor Grünert, the field of the invention of the present application is compositions suitable for hemodialysis. See paragraph 5 of the Declaration. Based on his years of experience working in the field of the invention, Professor Grünert considers himself an expert in that field. See paragraph 6 of the Declaration.

Professor Grünert has read and is familiar with the present application, including the claims of that application. He has also read the Official Action dated January 8, 2003 in the present application and Quarto di Palo et al. See paragraphs 7-9 of the Declaration.

At page 112, column 2, lines 9-11 of text under "Sir," Quarto di Palo et al. state:

> we have tried adding amino acids to the dialysis solution in a concentration equal to that of normal plasma.

The dialysis solution described by Quarto di Palo et al. does not contain the complete pattern of amino acids present in normal plasma. The dialysis solution described by Quarto di Palo et al. is missing Gln, Tyr, Cys, Asn, and Cit, all of which are present in normal plasma. See paragraphs 10 and 11 of the Declaration.

In 1978, when Quarto di Palo et al. was published in the scientific literature, the complete amino acid composition of normal plasma was well-known in the art. That this is so is demonstrated by Meister, A. (ed.), Biochemistry of the Amino Acids, Second Edition, Vol. 1, pp. 110 (1965). A copy of pages 108-117 of that reference text is attached hereto. See paragraph 12 of the Declaration.

In addition, the Table at the top of page 113 of Quarto di Palo et al. explicitly stated that Cit (citrulline), Cys (cystine), and Tyr (tyrosine) are present in normal plasma at a

specified range, but are not present in the dialysis solution described in that reference. See paragraph 13 of the Declaration.

At the time the present application was filed in 1999, one of ordinary skill in the field of the invention would have interpreted Quarto di Palo et al. to suggest that if an amino acid is used in the dialysis solution, then it should be used at a concentration in the range for normal plasma. See paragraph 14 of the Declaration.

Significantly, however, since the amino acids Gln, Tyr, Cys, Asn, and Cit were not used by Quarto di Palo et al., and those amino acids were well-known as components of normal plasma at the time that reference was published, one of ordinary skill in the field of the invention reading that reference at the time the present application was filed in 1999 would have concluded that Quarto di Palo et al. did not consider those amino acids to be useful components of a dialysis solution, even though they were known components of normal plasma. Otherwise, Quarto di Palo et al. would have used those amino acids in the dialysis solution described in that reference. See paragraph 15 of the Declaration.

In view of the foregoing, Quarto di Palo et al. would not have suggested to one of ordinary skill in the art in the field of the invention at the time the present application was filed in 1999 to modify the dialysis solution described by Quarto di Palo et al. by including Gln, Tyr, Cys, Asn, and Cit. This is because one skilled in the art would have recognized in 1999 that if Quarto di Palo et al. considered those amino acids to be useful components of a dialysis solution, then Quarto di Palo et al. would have included them in the dialysis solution described in that reference. Since those amino acids were well-known components of normal plasma in 1978 at the time that the Quarto di Palo et al. reference was published, the fact that Quarto di Palo et al. failed to use Gln, Tyr, Cys, Asn, and Cit would have been considered one of ordinary skill in the art in the field of the invention at the time the present application

was filed in 1999 as a direct teaching away from the dialysis composition claimed in the present application. See paragraph 16 of the Declaration.

As described in the specification of the present application at pages 1-2, patients with impaired kidney function have imbalanced amino acid compositions. See paragraph 17 of the Declaration.

As noted above, the dialysis solution described by Quarto di Palo et al. is based on the amino acid content of normal plasma. See paragraph 18 of the Declaration.

However, as described in the specification of the present application at page 2, administering such a solution to the patient actually exacerbates the amino acid imbalance in the patients. As a result, the dialysis method like that described by Quarto di Palo et al. has not been adopted for routine therapy, and has been evaluated as too expensive and ineffective. That this is so is demonstrated by Tepper et al., The International Journal of Artificial Organs, Vol. 1, No. 4, 1981, pp. 208-210, a copy of which is submitted herewith. See paragraph 19 of the Declaration.

The dialysis solution described by Quarto di Palo et al. has the following disadvantages as compared to the dialysis composition claimed in the present application:

(a) the total concentration of the dialysis solution described by Quarto di Palo et al. is with 250 mg/L not sufficient to compensate for the concentration gradient of amino acids, and

(b) the total concentration with 407 mg/L of the composition claimed in the present application is isotonic with respect to plasma amino acid concentrations in healthy people. See Grünert et al., Infusiontherapie, 11, 12-15 (1984) and

Grünert et al., Anaesthesist, 33, 11-19 (1984), copies of which are submitted herewith.

See paragraph 20 of the Declaration.

Based on the foregoing, Quarto di Palo et al. fail to suggest the claimed method. Accordingly, Claims 1-4 and 20 are not obvious over that reference.

Applicants submit that the present application is condition for allowance. Early notice to this effect is earnestly solicited.

Respectfully submitted,

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